Improving Glycaemic Control with Current Therapies

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A considerable proportion of Type 2 diabetic patients suffer from hyperglycaemic symptoms and therefore experience reduced quality of life. Furthermore, increasing evidence suggests that poor glycaemic control is associated with a risk that late complications will develop. The traditional stepped approach to therapy often results in a reluctance to escalate therapy to keep up with the progression of the disease, and therefore new strategies are needed to improve the results. Type 2 diabetes is a heterogeneous disorder, and hyperglycaemia is the result of deficient insulin secretion and insulin resistance; and the natural course of the disease is progression of hyperglycaemia. The therapy should be tailored to match the different needs of individual patients. Diet and exercise are essential to support all other therapies, but are often overlooked and may not be effective alone. The effectiveness of oral hypoglycaemic agents (OHAs) depends on the patients having sufficient insulin secretory capacity. These agents are therefore of little benefit to patients with profound β-cell failure. The combination of oral agents from two different pharmaceutical groups can be more effective than monotherapy, but in many patients insulin deficiency ensues and hyperglycaemia progresses. In principle, insulin therapy should always be able to lower glucose levels; improved glycaemic control is achieved in most patients, followed by amelioration of hyperglycaemic symptoms and improvements in quality of life. However, near-normoglycaemia may be difficult to achieve with the pharmacological limitations imposed by the preparations available, the methods of administration, and the ability and motivation of the patients. Importantly, insulin therapy should be tailored to meet the individual needs of the patients, and patients should be taught self-adjustment of doses based on self-monitoring of blood glucose levels. A considerable proportion of Type 2 diabetic patients (primarily the young and lean) require multiple-dose regimens. Combination therapy with OHAs and insulin might offer an advantage to some patients, and a recent study from Finland suggests that the combination of bedtime insulin and daytime metformin may be superior to other bedtime insulin regimens. There is still some way to go to devise an optimal therapy for Type 2 diabetes.

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Introduction

Increasing evidence from epidemiological studies suggests that poor glycaemic control is associated with an increased risk of micro- and macrovascular complications of Type 2 diabetes and premature mortality.[1–6] In a 6-year prospective study by Ohkubo *et al.*,[7] improving glycaemic control prevented progression of retinopathy and nephropathy in Japanese patients with Type 2 diabetes. Another prospective study by Malmberg *et al.*,[8] showed that lowering blood glucose with insulin therapy in the early stages of, and in the months following, an acute myocardial infarction, reduced the 1-year mortality rate. Recently, the United Kingdom Prospective Diabetes Study (UKPDS) reported a reduction in microvascular complications with intensive blood glucose control.[9] There was evidence, albeit inconclusive, of a 16 % risk reduction ($p = 0.052$) for myocardial infarction, which included non-fatal and fatal myocardial infarction and sudden death. However, the difference in mean HbA_{1c} was only 0.9 % pt between the intensively treated group and the conventionally treated group. Furthermore, even though the mean HbA_{1c} throughout the study was 7.0 % in the intensively treated group, it was considerably higher during the last years of the study when the frequency of major end-points increased rapidly. This suggests that better glycaemic control could also have resulted in a significant reduction in macrovascular disease, compared with conventional treatment. In our view, good glycaemic control that aims to prevent late complications is reflected by HbA_{1c} levels less than 1.5 % above the upper reference limit for non-diabetic subjects, and fair control, which aims to ameliorate hyperglycaemic symptoms, is a HbA_{1c} less than 3 % above the upper reference limit. However, traditional

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therapy often fails to achieve near-normoglycaemia during the long term. In a recent survey from general practices in Norway, fewer than 50 % of 1242 patients with Type 2 diabetes had good glycaemic control, defined as HbA_{1c} <7.5 % (normal reference interval 4–6 %) and nearly one out of five had HbA_{1c} >9 % (Cooper J, personal communication and reference 10). In this population-based study, 27 % of Type 2 diabetic patients were treated with insulin and glycaemic control was poorest among these patients, compared with diet-only and tablet-treated patients. Similar findings have been obtained in numerous cross-sectional and longitudinal studies published during recent years.[11–14] Improving glycaemic control among patients with Type 2 diabetes is therefore of great importance. Traditionally, a stepped approach is applied when treating hyperglycaemia in Type 2 diabetes (Figure 1). The main problem with this approach is the reluctance to escalate therapy at a pace needed to keep up with progression of the disease.

Pathogenesis of Hyperglycaemia: Implications for Therapy

Hyperglycaemia in Type 2 diabetes is caused by deficient insulin action, which is the result of a reduced insulin secretory capacity in pancreatic β-cells combined with insulin resistance in the peripheral tissues and the liver.[15] The relative contribution of these three mechanisms to hyperglycaemia differs among patients and therefore therapy should aim to correct the dominant disorder in the individual patient. Furthermore, the natural course of Type 2 diabetes is progression of hyperglycaemia and treatment must be modified according to the different stages of the disease.

The therapeutic options available today enable the clinician to tailor the therapy only to a limited degree, e.g. sulphonylurea tablets (SU) that increase glucose stimulated insulin secretion are rational to use when insulin deficiency predominates (i.e. primarily in lean and relatively insulin sensitive patients). However, a considerable proportion of lean and insulin sensitive patients have signs of autoimmune β-cell destruction and have, in fact, slowly developing Type 1 diabetes mellitus.[16,17] Furthermore, as the genetic and pathophysiological aspects of several different forms of maturity-onset diabetes of the young (MODY) have now been elucidated, some of the patients that develop Type 2 diabetes after the age of 25 may have MODY with dominating insulin deficiency.[18]

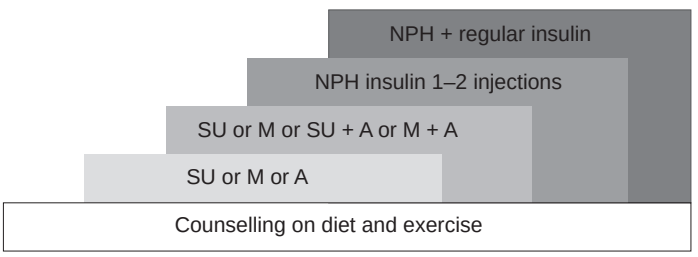

Figure 1. Traditional stepped approach to therapy in Type 2 diabetes. Lifestyle counselling on diet and exercise should continue when pharmacological agents are added. SU = sulphonylureas, M = metformin, A = acarbose, NPH = intermediate-acting insulin

Improving Glycaemic Control with Lifestyle Counselling

Although improvement of insulin resistance, and hence of glycaemic control, may be achieved by weight reduction and increased physical activity,[19] only a limited number of patients maintain good long-term glycaemic control with non-pharmacological therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), diet alone maintained fasting blood glucose ≤ 6 $mmol \cdot l^{-1}$ for 3 years in only 3 % and 4 % of non-obese and obese patients, respectively.[20] Drug-assisted weight loss (e.g. D-fenfluramine, sibutramine, tetrahydrolipostatin, fluoxetine) or very low calorie diets may be considered when diet fails to reduce weight, although these treatments are costly and the long-term outcome is uncertain. While the use of D-fenfluramine has been restricted due to side-effects, recent studies with the new lipase inhibitor tetrahydrolipostatin has showed promising results.[21] The drug has also been tested in a one-year placebo controlled trial in Type 2 diabetic patients, but despite a significant larger weight reduction than placebo, the effect on glycaemic control was quite moderate.[22] However, lifestyle modifications with diet, exercise and reduced smoking may exert important effects on the risk for atherosclerotic diseases in diabetic patients.[23] To accomplish such modifications, modern principles in modifying health behaviour must be used, e.g. motivating patients by working in groups. Through such means, a significant improvement in insulin sensitivity was shown in a controlled study over 1 year in more than 200 subjects with the 'insulin resistance syndrome'.[24]

Improving Glycaemic Control with Oral Antihyperglycaemic Agents

The effectiveness of all available oral hypoglycaemic agents (OHAs) presupposes that patients have sufficient insulin secretory capacity. Therefore, the maintenance of good glycaemic control over several years using OHAs in patients that have hyperglycaemia primarily caused by β-cell failure, e.g. in patients with signs of autoimmune β-cell destruction, cannot be expected. Furthermore, in Type 2 diabetic patients, where insulin resistance dominates, failure of OHAs to control hyperglycaemia occurs in most patients after 10–20 years,[11–14] mainly as a result of progressive loss of β-cell function.[11] Inadequate control of hyperglycaemia is not caused by a 'drug failure' but rather by the natural progression of Type 2 diabetes.[13,14] Despite a continuous increase in HbA_{1c} after the initial response observed following the introduction of

SU therapy, the SU was still active, i.e. when stopping SU therapy, hyperglycaemia worsened dramatically (Figure 2). Also, in patients on metformin monotherapy, hyperglycaemia increases with duration of the disease.[14,25]

The combination of two OHAs is more effective than monotherapy in maintaining good glycaemic control and should be initiated as soon as the combination of lifestyle counselling and one pharmacological agent fails to achieve the goal of glycaemic control. The use of agents that work through different antihyperglycaemic mechanisms is rational. Most commonly, metformin is added when SU treatment fails; this combination lowers glucose levels effectively[26] and may improve other metabolic parameters.[27] However, a word of warning concerning combination therapy is needed, because results from the recently published UKPDS show that the addition of metformin to SU was associated with an increased risk of death from both diabetes-related and other causes.[25] This finding contradicts the results obtained with each drug alone, and is difficult to explain. For the time being, we have to await further investigations on the matter. Although less well documented, addition of acarbose to SU may be as effective as metformin in reducing blood glucose levels.[28] However, addition of acarbose in a patient already treated with SU and metformin probably provides little extra effect on blood glucose levels, complicates the therapy and increases the costs. Despite the initial effect of combination therapy, insulin deficiency occurs and hyperglycaemia progresses in many patients.

Improving Glycaemic Control with Insulin

As the hyperglycaemia associated with Type 2 diabetes is caused by impaired insulin action, insulin therapy should, in principle, always be able to reduce blood glucose levels. Insulin therapy is rational to use in the majority of patients because insulin deficiency develops in most individuals with Type 2 diabetes over the course of the disease. However, achieving optimal glycaemic control may be difficult with the limitations imposed by the insulin preparations available, the modes of administration and the ability and motivation of the patients to comply with treatment objectives.

Initial treatment usually consists of two daily doses of intermediate-acting insulin and, as no algorithm exists that effectively predicts the insulin dose required to reach near-normoglycaemia in the individual patient, patients must be taught self-adjustment of doses. The evening dose of insulin is usually recommended to be increased first until the desired morning fasting glucose level is reached, followed by adjustment of the morning dose as required. When two doses of intermediate-acting insulin fail to control hyperglycaemia, regular insulin should be added. Although some studies have found that two and four daily doses of insulin are equally effective in controlling glycaemia,[29] research by Abraira *et al.*,[30] and our own observations, contradict these results. Often, the main problem with using two doses of intermediate-acting insulin is hyperglycaemia in the late afternoon and at night, before bedtime insulin is effective. When converting from oral treatment with a SU to two doses of intermediate-acting insulin, we found that glycaemia was reduced overall, but glucose levels in the evening did not change (Figure 3a). Increasing the morning dose does not effectively treat hyperglycaemia in the evening and results in hypoglycaemia before dinner. Adding regular insulin before dinner (at 4–6 PM) usually solves the problem, as illustrated in Figure 3b.

Another problem frequently encountered is marked hyperglycaemia after breakfast. Treatment options in this situation are to change to a regular multiple-dose regimen with regular insulin three times daily before main meals or administering premixed insulin before breakfast. When using regular insulin in Type 2 diabetic patients, a major problem is the slow and variable absorption from subcutaneous tissue. In a study of 12 patients with Type

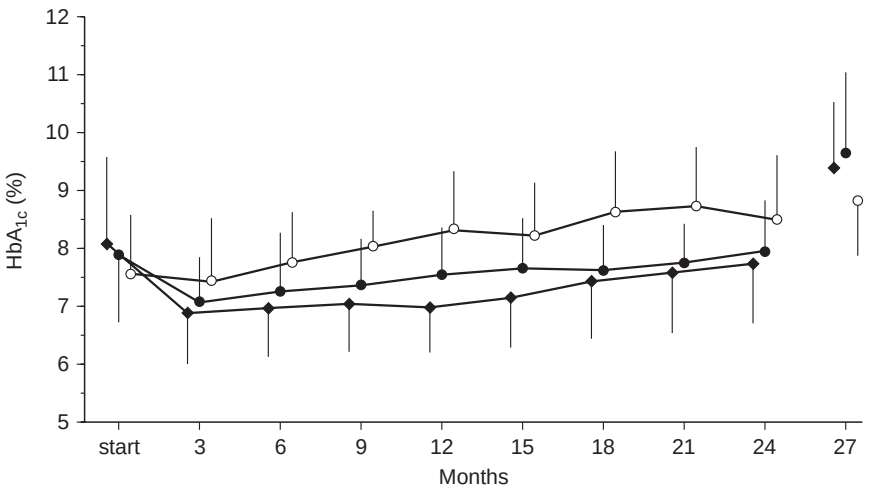

Figure 2. Mean (SEM) HbA_{1c} during 2 years of therapy with glipizide (●), glibenclamide (◆) or placebo (○), and 3 months after stopping the drugs in Type 2 diabetic patients

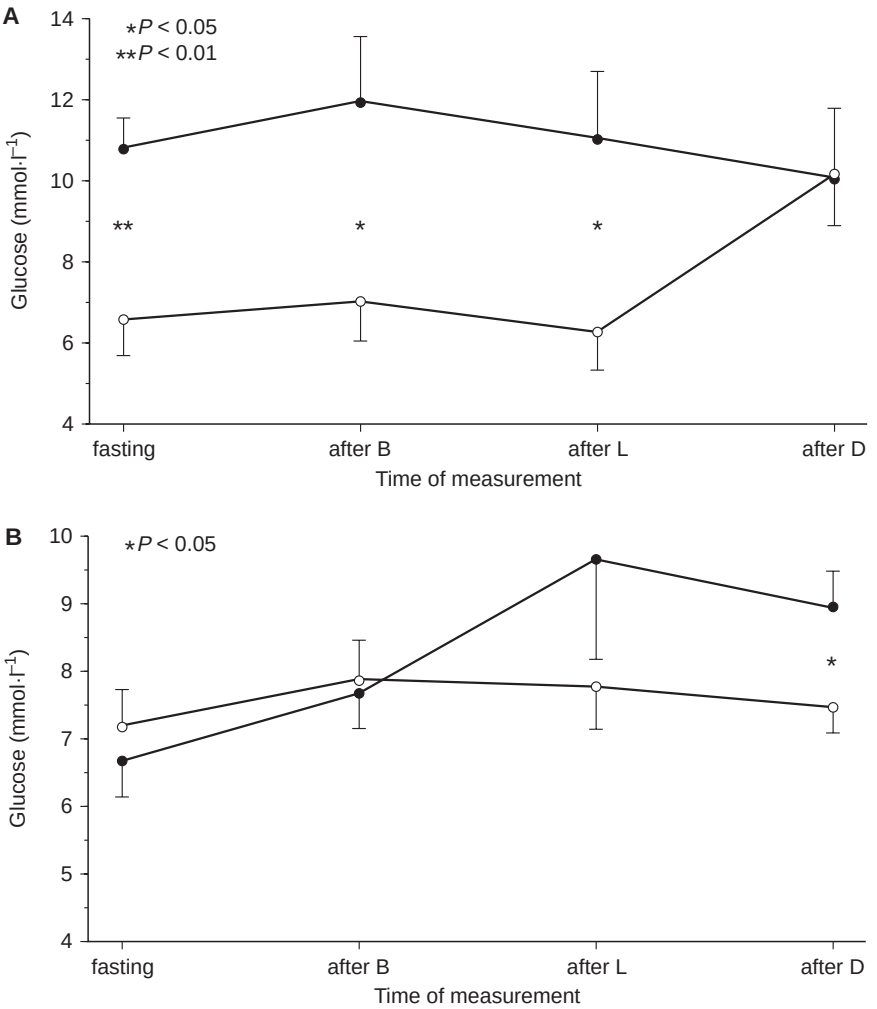

Figure 3. Mean (SEM) blood glucose levels in the fasting state, 2 h after breakfast (after B), 2 h after lunch (after L) and 2 h after dinner (after D) in patients with Type 2 diabetes. (**A**) 6 patients on maximum SU doses (●) and 6 months after changing to two doses of intermediate-acting insulin (○). (**B**) 5 patients on 2 doses of intermediate-acting insulin (●) and 6 months after adding regular insulin before dinner (○). $*P < 0.05$; $**P < 0.01$

2 diabetes, we found that injection of 0.15 $U \cdot kg^{-1}$ of regular insulin 30 min before a standard breakfast resulted in highly variable changes in serum insulin levels (Figure 4). The increase in serum insulin ranged from 20 to 240 $pmol \cdot l^{-1}$ after 30 min and from 0 to 480 $pmol \cdot l^{-1}$ after 120 min, reflecting both variable absorption of subcutaneously injected insulin and variable endogenous insulin secretion. In fact, according to one study, only 30–40 % of the regular insulin dose administered was absorbed 3 h after subcutaneous injection in the abdominal wall of obese Type 2 diabetic patients.[31] The introduction of the new rapid-acting insulin analogue insulin lispro may be an advantage, although absorption characteristics in Type 2 diabetic patients have not been published. In a study of 722 patients with Type 2 diabetes, insulin lispro resulted in less pronounced glucose excursions after a meal than regular insulin[32] but, despite this effect, overall glycaemic control was similar between the two regimens. This indicates that when using a rapid acting analogue in Type 2 diabetic patients, these patients may benefit from an insulin regimen that also covers the insulin requirement between meals.

Two main problems are encountered with insulin therapy in Type 2 diabetic patients, i.e. weight gain and hypoglycaemia. Additionally, Stout has highlighted possible atherogenic effects of hyperinsulinaemia.[33] However, the peripheral hyperinsulinaemia that results from insulin therapy has not been proven to contribute to the high prevalence of cardiovascular disease in Type 2 diabetic patients[34] and insulin therapy in the DIGAMI study lowered rather than increased cardiovascular events.[8] No evidence has been found from the UKPDS that therapy that increases insulin levels (e.g. SU or insulin therapy) results in more cardiovascular disease. However, it is still possible that the lack of any beneficial effects from intensive treatment on macrovascular complications might be because of the adverse effects of SU or insulin therapies (e.g. weight gain), which reduce the beneficial effects of improved glycaemic control. Hypoglycaemia is observed less frequently than in Type 1 diabetes mellitus but may have serious consequences

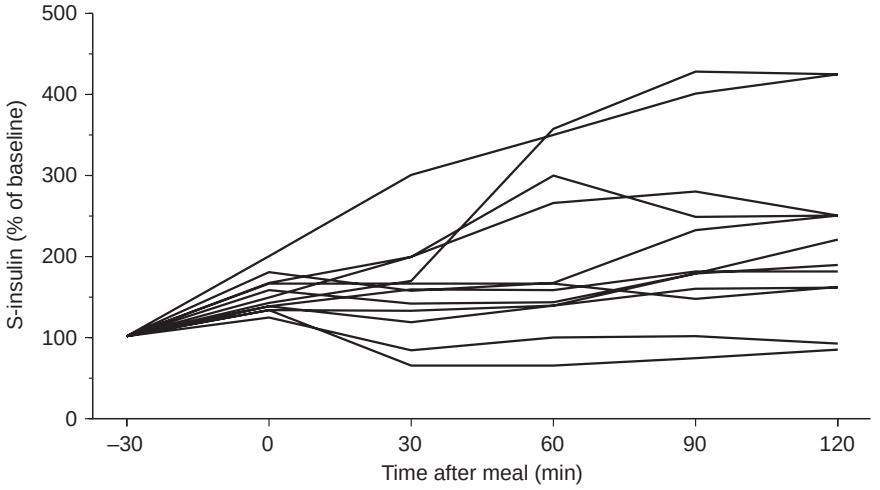

Figure 4. Serum insulin (fasting morning value = 100 %) before and during a standard breakfast in 12 patients with Type 2 diabetes given 0.15 U·kg^{-1} regular insulin subcutaneously in the abdominal wall 30 min before the meal. Each line represents one individual

in these patients because they are often elderly and some have considerable co-morbidity, especially from coronary and cerebrovascular disease. Weight gain is common when initiating insulin therapy in Type 2 diabetic patients.[9,13,14] In our hands, patients gained an average of 4 kg in the first year of insulin therapy and 6.5 kg (range 0–15 kg) during 5 years. However, in the Veterans Affairs Cooperative Study,[30] no significant weight gain was observed in patients treated intensively, probably as a result of dietary counselling throughout the study period.

Improving Glycaemic Control with Combination Therapy

The rationale for using combination therapy with OHAs and insulin is achieving glycaemic control and avoiding the problems that might follow insulin therapy, i.e. weight gain, hypoglycaemia and pronounced hyperinsulinaemia. Two meta-analyses have examined the effect on hyperglycaemia of combining insulin and SU therapy.[35,36] Both studies found that combination of a SU with insulin was more effective than insulin alone, although these studies had small sample sizes and were of short duration. A recent study by Yki-Järvinen *et al.*, indicates that the combination of bedtime intermediate-acting insulin and daytime metformin may be superior to insulin alone in reducing hyperglycaemia.[37] Furthermore, combination treatment resulted in minimal increases in body weight, in contrast to insulin alone or in combination with a SU. One reason for the excellent glycaemic control obtained in the insulin–metformin group may be that the patients were instructed to adjust their bedtime insulin doses according to an easy algorithm based only on their fasting morning glucose measurements. Acarbose can be added to insulin therapy to improve glycaemic control and lower required insulin doses although the effects obtained seem to be rather minor.[38]

Improving Glycaemic Control with Home Glucose Monitoring

While home blood glucose monitoring (HBGM) is an essential part of treating patients with Type 1 diabetes mellitus, doubt has been raised over whether it is useful in Type 2 diabetes.[39] However, when aiming at near-normoglycaemia, HBGM is important in the management of Type 2 diabetes. In addition to educating patients to measure their own blood glucose, they must also know when and why to measure, how to interpret the results and review the results when consulting the doctor or the diabetes nurse. The reason why some previous cross-sectional studies did not find improved glycaemic control among patients who practised HBGM compared with those who did not may be the result of an inadequate monitoring programme. Furthermore, patients who perform HBGM will often have more severe diabetes, i.e. longer duration, be treated with insulin and have late complications. The monitoring programme for patients performing HBGM should be tailored to the needs of the individual patient (Table 1) and only in this way can most patients benefit during the long term.

Table 1. Suggested programme for regular home blood glucose monitoring (HBGM) in patients with Type 2 diabetes, related to current treatment. Furthermore, patients should monitor themselves when they suspect hypoglycaemia, change food or exercise habits or have intercurrent illnesses

Treatment	Home blood glucose monitoring (HBGM)
Diet or oral hypoglycaemic agents	Fasting
Two doses of NPH insulin	Fasting and pre-dinner
Multiple doses or combination therapy	Fasting, pre-meal and at bedtime

Conclusion

Successful treatment of Type 2 diabetes depends on different factors from Type 1 diabetes and the patient's motivation, awareness and medical attention are important determinants.[40] Therapy should be tailored to meet the needs of individual patients, bearing in mind that in most patients insulin deficiency will occur eventually. Although this review has focused on the treatment of glycaemia, it must not be forgotten that the treatment of Type 2 diabetes involves much more than reducing blood glucose levels. Advocating cessation of smoking, controlling blood pressure and lipid levels and prescribing aspirin are all tools that may prevent cardiovascular disease in these high-risk patients. When it comes to glucose-lowering therapy, lifestyle modifications and oral agents are of primary importance in the early intervention strategies. Oral agents should therefore be used in the early stages when endogenous insulin is still available. Insulin therapy can improve glycaemic control in most patients, even though some require multiple-dose regimens or combination therapy. However, the effectiveness of insulin therapy and OHAs is decreased because of the less than optimal pharmacokinetic properties of the preparations available. Improvement of glycaemic control in Type 2 diabetic patients in the future therefore requires new strategies in implementing the therapeutic tools available today and new pharmacological agents that match the needs of the individual patient.

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